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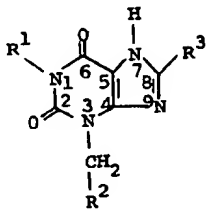
(54) Xanthine derivatives

(57) Xanthine derivatives of the general formula:



wherein R^1 and R^3 each represent an alkyl group containing from 1 to 6 carbon atoms, and R^2 represents a cyclohexenyl, furyl, tetrahydrofuryl or thienyl group, and pharmacologically-acceptable salts thereof formed with an alkali metal or a nitrogen-containing organic base, are useful in the treatment of respiratory and cardiovascular conditions.

They are prepared by cyclisation of the appropriate 5-alkanoylamino-6-amino uracil, or by reacting the appropriate substituted 5,6-diaminouracil with an anhydride of the acid R^3–COOH. The preparation of the *starting materials* and corresponding *5-nitroso-6-aminouracils* is described.

SPECIFICATION

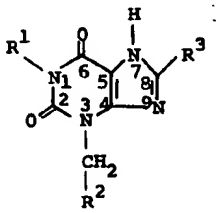
Xanthine derivatives

This invention relates to new therapeutically useful xanthine derivatives, to processes for their preparation and pharmaceutical compositions containing them.

It is well known that some xanthine derivatives, for example theophylline (i.e. 1,3-dimethylxanthine), have useful therapeutic properties.

It has now unexpectedly been found after research and experimentation that xanthine derivatives with alkyl substituents on the nitrogen and carbon atoms in the 1- and 8-positions respectively coupled with a cyclohexenylmethyl, furylmethyl, tetrahydrofurylmethyl or thienylmethyl substituent on the 3-position nitrogen atom possess outstanding pharmacological properties useful in the treatment of respiratory and cardiovascular conditions.

The xanthine derivatives of the present invention are accordingly those compounds of the general formula:

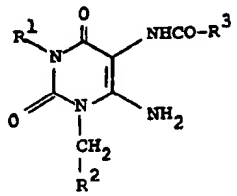


I

wherein R^1 and R^3 each represent an alkyl group containing from 1 to 6 (preferably at most 4) carbon atoms, and R^2 represents a cyclohexenyl, furyl, tetrahydrofuryl or thienyl group, and pharmacologically acceptable salts thereof formed with an alkali metal or a nitrogen-containing organic base.

Preferred compounds of general formula I are those wherein R^2 represents a cyclohex-3-enyl, 2-furyl, 2-tetrahydrofuryl or 2-thienyl group, and R^1 and R^3 are as hereinbefore defined and, more particularly, those wherein R^1 represents a methyl group. Of outstanding interest are 1,8-dimethyl-3-(cyclohex-3-enylmethyl)-xanthine, 1,8-dimethyl-3-(2-furylmethyl)-xanthine, 1-methyl-3-(cyclohex-3-enylmethyl)-8-isopropylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-sec-butylxanthine, 1,8-dimethyl-3-(2-tetrahydrofurylmethyl)-xanthine, 1-methyl-3-(2-furylmethyl)-8-ethylxanthine and 1,8-dimethyl-3-(2-thienylmethyl)-xanthine and, more especially, the two first-mentioned compounds.

According to a feature of the present invention, the xanthine derivatives of general formula I are prepared by cyclizing a uracil compound of the general formula:

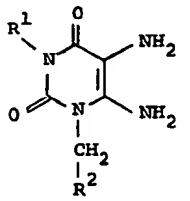


II

(wherein R^1, R^2 and R^3 are as hereinbefore defined) by application of methods known *per se*, for example by heating with an aqueous solution of sodium or potassium hydroxide, preferably at the boiling point of the reaction mixture. After acidification of the reaction mixture the xanthine product of the general formula I is isolated in manner known *per se*.

By the term "methods known *per se*" as used in this specification and accompanying claims is meant methods heretofore used or described in the literature.

The 5-acylamido-uracil starting materials of general formula II are obtained by reaction of a corresponding 5,6-diaminouracil of the general formula:



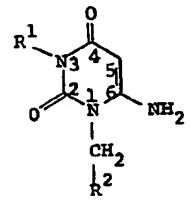
III

(wherein R^1 and R^2 are as hereinbefore defined) with a carboxylic acid of the general formula:

R^3–COOH IV

(wherein R^3 is as hereinbefore defined) at a temperature between 100° and 180°C. An excess of acid must be used, and preferably at least two moles of carboxylic acid are employed per mole of 5,6-diaminouracil.

The 5,6-diaminouracils of general formula III can be prepared from a corresponding 6-aminouracil of the general formula:



IV

(wherein R^1 and R^2 are as hereinbefore defined) by reaction with a mixture of sodium nitrite and acetic acid at a temperature between 10°C and 80°C to give the corresponding 5-nitroso derivative, and reduction of the 5-nitroso compound with sodium dithionite in ammonium hydroxide aqueous solution at a temperature between 40°C and 90°C to the diamino compound.

The 6-aminouracils of general formula V can be prepared from the corresponding N,N'-disubstituted-urea by methods known *per se*, e.g. V. Papesch and E.F. Schroeder, J. Org. Chem., *16*, 1879–90, (1951).

The xanthine derivatives of general formula I are also prepared, according to a further feature of the present invention, from a corresponding 5,6-diaminouracil of general formula III by heating with an excess of the anhydride of the corresponding carboxylic acid of general formula IV, preferable at the boiling point of that anhydride. In this case the 5-acylamido derivatives of general formula II is not isolated as the xanthing derivative of general formula I is obtained directly.

The xanthine products of general fomula I obtained by the aforedescribed processes can be purified by application of methods known *per se*, for example by recrystallization from an organic solvent, e.g. methanol, ethanol, isopropanol, tetrahydrofuran, dioxan or ethyl acetate.

The compounds of general formula I exhibit pharmacological properties useful in the treatment of respiratory and cardiovascular conditions such as bronchal asthma, reversible obstructive respiratory disease, and obstructive peripheral and cardiac vascular disease. Thus they relax bronchial smooth muscle both *in vitro* and *in vivo* and inhibit the bronchoconstriction induced by histamine, acetylcholine and other smooth muscle stimulants. Furthermore, this direct bronchodilator activity is accompanied by inhibitory activity against the liberation of histamine and other autacoids in response to appropriate anaphylactic challenges. They also relax the smooth muscle of peripheral and coronary blood vessels resulting in vasodilation, an increase in blood flow and a fall in blood pressure unaccompanied by tachycardia.

Stimulant effects on the central nervous system are minimal as are other xanthine-like actions such as the induction of diuresis.

Experiments have been carried out with some xanthine derivatives of the present invention in order to compare their pharmacological properties with those of theophylline and 1-methyl-3-furfuryl-xanthine, a compound (referred to later herein as Compound 1) prepared by K.R.H. Wo ldridge and R. Slack, J. Chem. Soc. *1962*, 1863–1868, b th compounds being related to the xanthine derivatives f general formula I but having n substituent on the 8-position carb n atom.

The c mpounds of general formula I tested were 1,8-dim thyl-3-(2-furlmethyl)-xanthine (R^1 and $R^3 = CH_3$ and R^2 = 2-furyl; referred to in the following Tabl s as C mpound 2; 1-methyl-3-(2-furylmethyl)-8-ethylxanthine ($R^1 = CH_3$, $R^3 = C_2H_5$ and R^2 = 2-furyl; C mpound 3); 1,8-dim thyl-3-(cyclohex-3-enylmethyl)-xanthine (R^1 and $R^3 = CH_3$ and R^3 = cyclohex-3-enyl;

C mpound 4);

1-methyl-3-(cycl hex-3-enylmethyl)-8-isopropylxanthin ($R^1 = CH_3$, $R^3 = isoC_3H_7$ and R^2 = cyclohex-3-enyl; Compound 5);

1,8-dimethyl-3-(2-tetrahydrofurylmethyl)-xanthine (R^1 and $R^3 = CH_3$ and R^2 = 2-tetrahydrofuryl; Compound 6);

1-methy-3-(2-tetrahydrofurylmethyl)-8-sec-butylxanthine ($R^1 = CH_3$, $R^3 = -CH(CH_3)CH_2CH_3$ and R^2 = tetrahydrofuryl; Compound 7), and

1,8-dimethyl-3-(2-thienylmethyl)-xanthine (R^1 and $R^3 = CH_3$ and R^2 = 2-thienyl; Compound 8).

The results obtained in the experiments with the various compounds are given in the following Tables.

TABLE 1

Compound	Antagonism to histamine induced broncho construction[1]	Vasodilator Activity[2]	Toxicity[3]
Theophylline	5	+	≃500
1	4	+ +	≃1000
2	10	+ + +	>100<500
3	9	+ + +	>100<500
4	6	+ + +	>500
5	6	+ + +	>500
6	6	+ + +	>500
7	6	+ + +	>500
8	6	+ + +	>100<500

(1) No. of guinea-pigs protected (group of 10) by 100 mg kg^{-1} p.os. of compound against the broncho-constrictor effects of enforced inhalation of nebulized histamine.

(2) Percentage reduction in peripheral resistance in the chloralose anaesthetised cat, + = 26–40; + + = 41–55; + + + = 56–70: induced by 3 mg kg^{-1} i.v.

(3) Approximate LD_{50} values (mg kg^{-1} p.os.) in the mouse.

Table 2 gives a comparison of the bronchodilator and antianaphylactic properties of the aforementioned specific compounds of general formula I with those of theophylline and Compound 1.

TABLE 2

Experimental model	Species	Theophylline	COMPOUND 1	2	3	4'	5	6	7	8
(1) Konzett and Rossler	Guinea-pig	6.5	5	2	4	0.7	2	5.5	2	1.7
(2) Isolated tracheal (*in vitro*)	Guinea-pig	10	7	2	4	1	6	7	2	3
(3) Passive cutaneous anaphalyaxis	Rat	+ +	+ +	+ + +	+ + +	+ +	+ +	+ + +	+ + +	+ +
(4) Schultz-Dale reaction in isolated ileum	Guinea-pig	5×10^{-4}	3×10^{-4}	1×10^{-4}	3×10^{-4}	3×10^{-5}	3×10^{-4}	1×10^{-5}	3×10^{-4}	3×10^{-5}

(1) Approximate ED_{50} (mg kg^{-1} i.v.) against bronchoconstriction induced by intravenous histamine (minimum 3 experiments).
(2) Approximate ED_{50} (μg ml^{-1} of organ bath fluid) for relaxation of tracheal smooth muscle (minimum 3 experiments).
(3) Activity at 100 mg kg^{-1} p.os. against the PCA reaction induced by serum taken from rats sensitized to ovalbumin (groups of 12).
(4) Molar concentration to inhibit both the induced contraction and the histamine released from ileum isolated from sensitized (ovalbumin) guinea pigs in response to a challenge with antigen (minimum 3 experiments).

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The experimental models referred to in Table 2 are described in the following publications:-

(1) Konzett, H. and Rossler, R., Arch. Exp. Path. Pharmakol., *195,* 71–74 (1940),
(2) Castillo, J.C. and De Beer, E.J., J. Pharmac. Exp. Ther., *90,* 104–109 (1947).
(3) Ovary, Z., Fed. Proc., *24,* 94 (1965),
(4) Dale, M.M. amd Zilletti, L., Br. J. Pharmac., *39,* 542–555 (1970).

It will be appreciated from the results of the experiments that the xanthine derivatives of general formula I with an 8-alkyl substituent are more active on the respiratory tract than the related xanthine compounds tested having hydrogen attached to the carbon atom in position 8. Thus, for example, Compounds 2 to 8 (which are compounds of the invention) are more active against histamine-induced bronchoconstriction than the previously described Compound 1 and theophylline. The compounds of the invention are also effective in other bronchodilator tests as well as in pharmacological models for antianaphylactic activity and again they are clearly more potent than theophylline as shown in Table 2.

The compounds of general formula I are also more active than theophylline as vasodilators (see Table 1). This vascular activity is not accompanied by a corresponding positive chronotropic effect on the heart, which makes the new compounds especially useful for treatment of obstructive cardiovascular disease. An additional advantage is that the compounds of general formula I have very long half-lives (e.g. Compounds 2 and 4 have mean half-lives in man of 52.8 and 13.2 hours respectively whereas the half-life of theophylline is only 3 hours).

In general the xanthine derivatives of general formula I will be useful for the treatment of obstructive respiratory disease and asthma on the one hand, and cerebral or cardiac vascular insufficiency on the other.

The xanthine derivatives of general formula I may also form pharmacologically-acceptable salts with alkali metals or nitrogen-containing organic bases whose salts are formed by reaction of the compounds of general formula I with an alkali metal hydroxide or a nitrogen-containing organic base using, for example, water, methanol or ethanol as a solvent at a temperature between 40° and 100°C.

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically-acceptable salt thereof as hereinbefore mentioned, in association with a pharmaceutically-acceptable carrier or diluent. Preferable the compositions are made up in a form suitable for oral, rectal or parenteral administration.

The pharmaceutically-acceptable carriers or diluents which are admixed with the active compound or compounds or salts of such compounds to form the compositions of this invention are well known *per se* and the actual excipients used depend *inter alia* on the intended method of administration of the compositions. Compositions of this invention are preferably adapted for administration *per os.* In this case, the compositions for oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations such as elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents if desired. Tablets or capsules may conveniently contain between 5 and 150 mg and preferably from 10 to 50 mg of active ingredient or the equivalent amount of a pharmacologically-acceptable salt thereof. The compounds may also be incorporated into pellets coated with appropriate natural or synthetic polymers known in the art to produce sustained release characteristics or incorporated with polymers into tablet form to produce the same characteristics.

The liquid compositions adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous or aqueous-alcoholic solutions of a soluble compound or salt thereof in association with, for example, sucrose or sorbitol to form a syrup. The suspensions may comprise an insoluble or micro-encapsulated form of an active compound of the invention in association with water and other acceptable solvents together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble compounds or salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

In human therapy, the doses of the xanthine derivatives depend on the desired effect and duration of the treatment; adult doses are generally between 15 mg and 150 mg per day. In general the physician will decide the posology taking into account the age and weight inrinsic to the patient being treated.

The following Examples illustrate the preparation of xanthine derivatives of the present invention.

EXAMPLE 1

To a suspensi n of 1-methyl-3-(2-furylmethyl)-6-aminouracil (260 g; 1.175 moles) and sodium nitrite (90 g; 1.3 moles) in water (1870 ml), acetic acid (141.5 ml) was sl wly added at a temperature f 20°C. The mixture was stirred f r 24 hours at this t mperature and then the resulting insoluble 1-methyl-3p-(2-furylmethyl)-5-nitroso-6-aminouracil was collected by filtration, washed with water, then with diethyl ether and dried (292.5 g; yield 99.3%); its melting point was 223–225°C.

A mixture of this 1-methyl-3-(2-furylmethyl)-5-nitroso-6-aminouracil (292.5 g; 1.169 moles) in concentrated ammonium hydroxide aqueous solution (4680 ml) was heated to 60°C and sodium dithionite (780 g; 3.71 moles) added portionwise; the colour of the mixture changed from violet to pale yellow. After cooling, the precipitated solid was collected by filtration, washed with water (4 litres), recrystallised from methanol, and dried to give 1-methyl-3-(2-furylmethyl)-5,6-diaminouracil (208 g; yield 75.3%), m.p. 168–170°C.

A mixture of this 1-methyl-3-(2-furylmethyl)-5,6-diaminouracil (11.8 g; 0.05 moles) and propionic acid (18.5 ml; 0.25 moles) was boiled under reflux for 2 hours. After cooling, a mixture of diethyl ether and isopropanol was added and 1-methyl-3-(2-furylmethyl)-5-propionamido-6-aminouracil crystallized (13 g; yield 89%). Its melting point after recrystallization from methanol was 238–240°C.

This compound (10 g; 0.0342 moles) was treated with a 2N sodium hydroxide aqueous solution (50 ml) and the mixture boiled under reflux for half an hour. After cooling the resulting solution, dilute hydrochloric acid was added until an acidic pH was attained and then the mixture was extracted with chloroform. The organic solution was washed with water, decolorized, dried (Na_2SO_4) and the solvent removed *in vacuo* to dryness. The solid residue was treated with diethyl ether and collected by filtration to give 1-methyl-3-(2-furylmethyl)-8-ethylxanthine (7.2 g; yield 76.7%), m.p. 233–235°C (after recrystallization from ethanol).

Also prepared in a similar manner using the appropriate starting materials were
1,8-dimethyl-3-(2-furlmethyl)-xanthine, m.p. 280–282°C;
1-methyl-3-(2-furylmethyl)-8-sec-butylxanthine, m.p. 128–129°C, and
1-methyl-3-(2-furylmethyl)-8-propylxanthine, m.p. 216–218°C.

EXAMPLE 2

A solution of 1-methyl-3-(2-furylmethyl)-5,6-diaminouracil (17.7 g; 0.075 moles) in acetic anhydride (150 ml) was boiled under reflux for 5 hours. After cooling, a solid crystallized which was collected by filtration and recrystallized from ethanol to give 1,8-dimethyl-3-(2-furylmethyl)-xanthine (14.2 g; yield 72.8%), m.p. 280–282°C.

EXAMPLE 3

A mixture of 1-(cyclohex-3-enylmethyl-3-methyl-5,6-diaminouracil (10 g; 0.04 mole) and glacial acetic acid (30 ml) was boiled under reflux for 2 hours. The solvent was removed by distillation *in vacuo* and the solid residue was collected with diethyl ether and filtered to give 1-(cyclohex-3-enylmethyl)-3-methyl-5-acetamido-6-aminouracil (11 g; yield 94%), m.p. 233–235°C.

This compound (11 g; 0.038 moles) was treated with a 10% sodium hydroxide aqueous solution (35 ml) and the mixture boiled under reflux for half an hour. After cooling the resulting solution, dilute hydrochloric acid was added until pH 5 was reached, and the mixture was then extracted with chloroform. The organic solution was washed with water, decolorized, dried (Na_2SO_4) and the solvent removed *in vacuo* to dryness. The solid residue was treated with diethyl ether and collected by filtration to give 1,8-dimethyl-3-(cyclohex-3-enylmethyl)-xanthine (8.5 g; yield 82%), m.p. 253°–255°C (after recrystallization from isopropanol).

Also prepared in a similar manner starting from the appropriate 5,6-diaminouracil and carboxylic acid were
1,8-dimethyl-3-(2-thienylmethyl)-xanthine, m.p. 297–299°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-sec-butylxanthine, m.p. 112–114°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-ethylxanthine, m.p. 191–193°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-propylxanthine, m.p. 184–186°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-isopropylxanthine, m.p. 177–179°C;
1-methyl-3-(cyclohex-3-enylmethyl)-8-sec-butylxanthine, m.p. 153–155°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-t-butylxanthine, m.p. 193–195°C;
1-methyl-3-(cyclohex-3-enylmethyl)-8-isopropylxanthine, m.p. 201–203°C;
1-methyl-3-(cycloh x-3-enylmethyl)-8-propylxanthine, m.p. 202–204°C;
1-methyl-3-(2-thienylm thyl)-8-sec-butylxanthine, m.p. 148–150°C;
1-methyl-3-(2-tetrahydrofurylmethyl)-8-butylxanthine, m.p. 156–158°C;
1-methyl-3-(cycloh x-3- nylm thyl)-8-t-butylxanthine, m.p. 203–205°C;
1-propyl-3-(2-tetrahydrofurylmethyl)-8-methylxanthine, m.p. 223–225°C, and
1-propyl-3-(cycl hex-3-enylmethyl)-8-methylxanthine, m.p. 207–209°C.

EXAMPLE 4

A solution of 1-(2-tetrahydrofurylmethyl)-3-methyl-5,6-diamino uracil (12 g; 0.05 moles) in acetic anhydride (100 ml) was boiled under reflux for 5 hours. After cooling, a greyish solid crystallized which was collected by filtration and recrystallized from ethanol to give 1,8-dimethyl-3-(2-tetrahydrofurylmethyl)-xanthine (9.3 g; yield 70.4%), m.p. 238–240°C.

EXAMPLE 5

A suspension of 1,8-dimethyl-3-(2-furylmethyl)-xanthine (229 g; 0.88 moles) (prepared as described in Example 2) in 10% sodium hydroxide aqueous solution (1100 ml) was boiled under reflux until dissolution was complete. On cooling, the sodium salt of 1,8-dimethyl-3-(2-furylmethyl)-xanthine (201 g; yield 81%) was obtained, m.p. >300°C.

The following Examples illustrate pharmaceutical compositions according the invention.

EXAMPLE 6

100,000 capsules each containing 100 mg of 1-methyl-3-(2-furylmethyl)-8-ethylxanthine were prepared from the following formulation:

1-methyl-3-(2-furylmethyl)-8-ethylxanthine	10kg
lactose monohydrate	8kg
corn starch	2kg
colloidal silicon dioxide	1kg
magnesium stearate	2kg

Procedure

The above ingredients were sieved through a 60-mesh sieve, then mixed in a suitable mixer and filled into 100,000 gelatine capsules (230 mg).

EXAMPLE 7

1000 bottles of suspension (capacity 150 ml) each containing 1500 mg of 1,8-dimethyl-3-(2-furylmethyl)-xanthine were prepared as follows:

1,8-dimethyl-3-(2-furylmethyl)-xanthine	1,500 g
microcrystalline cellulose	1,500 g
sodium carboxymethylcellulose	900 g
70% sorbitol aqueous solution	33,000g
glycerine	4,500 g
polysorbate 80	400 g
sodium methyl *p*-hydroxybenzoate	240 g
sodium propyl *p*-hydroxybenzoate	60 g
anti-foam silicone	150 g
sodium saccharin	300 g
flavouring	q.s.
demineralised water q.s.	150 litres

Procedure

To a solution of the sodium methyl *p*-hydroxy-benzoate, sodium propyl *p*-hyroxybenzoate and sodium saccharin in 30 litres of demineralised water, a wet-milled suspension of the sodium carboxymethylcellulose in glycerine was added. After stirring for 1 hour, a suspension of the microcrystalline cellulose in 60 litres of demineralised water was added and then the sorbitol solution, polysorbate 80, 1,8-dimethyl-3-(2-furylmethyl)-xanthine, anti-foam silicone and flavouring were successively added with stirring. The volume of the mixture was adjusted to 150 litres with demineralised water and the homogeneous suspension was filled into 150 ml bottles using an appropriate filling machine.

EXAMPLE 8

20,000 bottles of solution (capacity 150 ml) each containing 300 mg of 1,8-dimethyl-3-(cyclohex-3-enylmethyl)-xanthine were prepared as follows:

1,8-dimethyl-3-(cyclohex-3-enylmethyl-xanthine	6 kg
ethanol	45 kg
70% sorbitol aqueous solution	1,050 kg
sodium saccharin	3 kg
sodium carboxymethylcellulose	60 kg
flavouring	q.s.
demineralised water q.s.	3000 litres

Procedure

A solution of the sodium carboxymethylcellulose in 1000 litres of water and 5 kg of ethanol was added to another solution of the 1,8-dimethyl-3-(cyclohex-3-enylmethyl)-xanthine in 40 kg of ethanol and 500 litres of water at a temperature of 50°C. Then the sorbitol solution, sodium saccharin and flavouring were added and the volume of the mixture was adjusted to 300 litres with dimineralised water. After filtration, the solution was filled into 150 ml bottles using an appropriate filling machine.

EXAMPLE 9

10,000 suppositories each containing 150 mg of 1-methyl-3-(2-tetrahydrofurylmethyl)-8-sec-butyl-xanthine were prepared as follows:

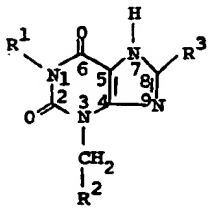
1-methyl-3-(2-tetrahydrofurylmethyl)-8-sec-butylxanthine	1,500g
theobroma oil	18,500g

The theobroama oil was melted and the active compound suspended in it. The mixture was then poured into appropriate suppository mould to make 2.0 g suppositories.

Instead of the xanthine derivatives specifically mentioned in Examples 5 to 8, there may be used in the pharmaceutical formulations described any other xanthine derivative within the scope of general formula I, for example those compounds of that formula referred to in Examples 1 to 3.

CLAIMS

1. Xanthine derivatives of the general formula:



wherein R^1 and R^3 each represent an alkyl group containing from 1 to 6 carbon atoms, and R^2 represents a cyclohexenyl, furyl, tetrahydrofuryl or thienyl group, and pharmacologically-acceptable salts thereof formed with an alkali metal or a nitrogen-containing base.

2. Xanthine derivatives according to claim 1 wherein R^2 represents a cyclohexenyl, tetrahydrofuryl or thienyl group, and R^1 and R^3 are as defined in claim 1, and pharmacologically-acceptable salts thereof formed with an alkali metal or a nitrogen-containing organic base.

3. Xanthine derivatives according to claim 1 wherein R^2 represents a cyclohex-3-enyl, 2-furyl, 2-tetrahydrofuryl or 2-thienyl group and R^1 and R^3 are as defined in claim 1, and pharmacologically-acceptable salts thereof formed with an alkali metal or a nitrogen-containing organic base.

4. Xanthine derivatives according to claim 1, 2 or 3 wherein the alkyl group represented by R^1 and R^3 contains from 1 to 4 carbon atoms.

5. Xanthine derivatives according to claim 1, 2, 3 or 4 wherein R^1 represents the methyl group.

6. 1,8-Dimethyl-3-(cyclohex-3-enylmethyl)-xanthin .

7. 1,8-Dim thy-3-(2-furylmethyl)-xanthin .

8. 1-M thyl-3-(cyclohex-3-enylmethyl)-8-isopropylxanthine.

9. 1-Methyl-3-(2-tetrahydrofurylmethyl)-8-sec-butylxanthine.

10. 1,8-Dim thyl-3-(2-t trahydrofurylmethyl)-xanthine.

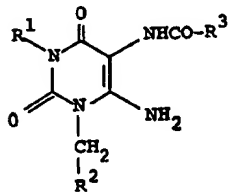
11. 1-Methyl-3-(2-furylmethyl)-8-ethylxanthine.

12. 1,8-Dimethyl-3-(2-thienylmethyl)-xanthine.

13. Pharmacologically-acceptable salts of a compound claimed in any one of claims 5 to 12 formed with an alkali metal or a nitrogen-c ntaining organic base.

14. 1-Methyl-3-(2-furylmethyl)-8-sec-butylxanthine, 1-methyl-3-(2-furylmethyl)-8-propylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-ethylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-propylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-isopropylxanthine, 1-methyl-3-(cyclohex-3-enylmethyl)-8-sec-butylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-t-butylxanthine, 1-methyl-3-(cyclohex-3-enylmethyl)-8-propylxanthine, 1-methyl-3-(2-thienylmethyl)-8-sec-butylxanthine, 1-methyl-3-(2-tetrahydrofurylmethyl)-8-butylxanthine, 1-methyl-3-(cyclohex-3-enylmethyl)-8-t-butylxanthine, 1-propyl-3-(2-tetrahydrofurylmethyl)-8-methylxanthine and 1-propyl-3-(cyclohex-3-enylmethyl)-8-methyxanthine, and pharmacologically-acceptable salts of any such compound formed with an alkali metal or a nitrogen-containing organic base.

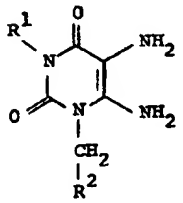
15. A process for the preparation of a xanthine derivative as claimed in claim 1 which comprises cyclizing a uracil compound of the general formula:



(wherein R^1, R^2 and R^3 are as defined in claim 1) by a method known *per se*.

16. A process according to claim 15 in which cyclization of the uracil compound is effected by heating with an aqueous solution of sodium or potassium hydroxide.

17. A process for the preparation of a xanthine derivative as claimed in claim 1 which comprises heating a 5,6-diaminouracil of the general formula:



(wherein R^1 and R^2 are as defined in claim 1) with an excess of an anhydride of a carboxylic acid of the general formula;

R^3–COOH

wherein R^3 is as defined in claim 1.

18. A process according to claim 15, 16 or 17 followed by the step of converting by a method known *per se* a xanthine derivative of the general formula specified in claim 1 thus obtained into a pharmacologically-acceptable alkali metal salt or a salt with a pharmacologically-acceptable nitrogen-containing organic base.

19. Xanthine derivatives of the general formula specified in claim 1 and pharmacologically-acceptable salts thereof with alkali metal and nitrogen-containing organic bases when prepared by the process claimed in any one of claims 15 to18.

20. Pharmaceutical compositions which comprise, as active ingredient, a xanthine derivative as claimed in any one of claims 1 to 12 and 14, or a pharmacologically-acceptable alkali metal salt thereof or a salt thereof formed with a pharmacologically-acceptable nitrogen-containing organic base, in association with a pharmaceutically-acceptable carrier or diluent.

21. Pharmaceutical compositions according to claim 20 substantially as hereinbefore described with especial reference to Example 6, 7, 8 or 9.

22. Xanthine derivatives of the general formula specified in claim 1, and pharmacologically-acceptable salts th r f f rmed with an alkali metal or a nitrog n-containing organic base, for therapeutic us in the treatment of respiratory and cardiovascular conditions such as br nchial asthma, reversible obstructiv respiratory disease and obstructiv periph ral and cardiac vascular disease.

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